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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,266	06/20/2003	Fumitoshi Asai	03337C/HG	7488

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
11/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,266	ASAI ET AL.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's filing of Remarks on 08/15/08. Applicant's argument over claims 1-5 have been fully considered but they are not persuasive.

2. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernat et al. (US 5989578) or Uchiyama et al. (Stroke, Vol. 20, No. 12, pp. 1643-1647) in view Asai et al. (Anuual Report of Sankyo Research Laboratories, 1999, 51, pp. 1-44).

Bernat or Uchiyama teaches a combination of ADP receptor blocking antiplatelet drug (i.e., clopidogrel or ticlopidogrel) and aspirin that shows the synergistic effects. Bernat discloses 1 to 500mg per clopidogrel or ticlopidogrel to 1 to 500mg per aspirin (column 3, lines 21-28; column 4, lines 18-32; Tables; claims) and Uchiyama whereas Uchiyama discloses 300mg per aspirin and 200 mg per ticlopidine ("Results" and "Discussion).

Asai teaches that CS-747 (which is 2-acetoxy-5-(alpha-cyclopropylcarbonyl-2-fluorobenzyl)-4-5,6,7-tetrahydrothieno[3,2-c]pyridine) is effective as ADP receptor blocking antiplatelet agent without any serious adverse effects and more potent than ticlopidine or clopidogrel (see especially page 10-43).

The teaching of Bernat or Uchiyama mainly differs from the claimed invention in the use of 2-acetoxy-5-(alpha-cyclopropylcarbonyl-2-fluorobenzyl)-4-5,6,7-tetrahydrothieno[3,2-c]pyridine to prepare said combination. To incorporate teaching of Bernat or Uchiyama, would have been obvious in view of Asai who teaches the advantage of using CS-747 (which is 2-acetoxy-5-(alpha-cyclopropylcarbonyl-2-fluorobenzyl)-4-5,6,7-tetrahydrothieno[3,2-c]pyridine)

over ticlopidine or clopidogrel for potency consideration and better safety and tolerability profile.

One having ordinary skill in the art would have motivated to select CS-747 (which is 2-acetoxy-5-(alpha-cyclopropylcarbonyl-2-fluorobenzyl)-4-5,6,7-tetrahydrothieno[3,2-c]pyridine with the expectation that substitution of ticlopidogrel or clopidogrel with CS-747 would not significantly alter the analogous property of the compound of the reference having ADP receptor blocking antiplatelet agent while providing better safety and tolerability profile to the patient over ticlopidogrel or clopidogrel. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the instant "ratio by weight of 1:500 to 500:1", those of ordinary skill in the art would have readily optimized effective dosages as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed in the cited references.

4. Claims 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernat et al. (US 5989578) or Uchiyama et al. (Stroke, Vol. 20, No. 12, pp. 1643-1647) in view Asai et al.

(Anuual Report of Sankyo Research Laboratories, 1999, 51, pp. 1-44), and further in view of Koike et al. (US 5288726). See rejection above.

The modified teaching of Bernat or Uchiyam mentioned above (Bernat et al. or Uchiyama et al. in view of Asai et al.) includes all that is recited in claims 4-5 except the use of the specific salt form, namely hydrochloride or maleate.

However, it would have been obvious in view of Koike who teaches compounds represented by formula (I) including 2-acetoxy-5-(alpha-cyclopropylcarbonyl-2-fluorobenzyl)-4-5,6,7-tetrahydrothieno[3,2-c]pyridine, wherein said compounds are prepared in pharmaceutically salts thereof including maleate and hydrochloride (abstract; column 13, lines 43-63; column 22, line 19 and Example 23).

One having ordinary skilled in the art would have been motivated to select the claimed compounds in maleate or hydrochloride salt with reasonable expectation of success that preparation of said composition in maleate and hydrochloride salt form would not significantly alter the analogous properties of compound of the reference due to close structural similarity of the compounds.

Response to Arguments

4. As indicated above, applicant's arguments filed 08/15/08 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that the examiner's rejection relies in part on the reasoning that Uchiyama discloses a combination ticlopidine and aspirin duplicates the teaching in the earlier rejection from Bernat. Applicant asserts that Uchiyama

represents a cumulative reference. Furthermore, applicant asserts that the examiner rejection relies on Asai which discloses CS-747 duplicates the teaching in the earlier rejection from Koike.

This argument is not found persuasive. Sole basis of the examiner's withdrawal of rejections of claims 1-3 over Ogletree in view of Bernat et. al. or claims 4-5 and 18-19 over Ogletree in view of Bernat and further in view of Koike et al. under 35 USC 103(a) was inventor's Declaration filed 10/22/07 which predated the Ogletree reference. As indicated in the previous Office Action mailed 05/30/2008, the notice of allowance was withdrawn upon further consideration in light of the submitted IDS filed 05/12/2008 and/or Asai et al. (Anuual Report of Sankyo Research Laboratories, 1999, 51, pp. 1-44).

Unlike the applicant's argument, the instant rejection(s) is/are not entirely based on the repetitive reference(s) that was/were either previously relied upon on discussed in a prior Office proceeding. Rather, the instant rejection requires the Asai reference which never has been discussed. As discussed in the previous Office Action mailed 05/30/08, Asai provides an ample motivation to arrive at the instant invention under the meaning of 103(a). Thus, the examiner maintains the rejection of the record.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one having ordinary skill in the art would have expected as taught by Asai that CS-

747 is more potent than ticlopidine or clopidogrel as ADP receptor blocking antiplatelet agent while providing better safety and tolerability profile to the patient. Thus, one having ordinary skill in the art would have been motivated to combine the references and make the modification to arrive at the instant combination with better safety and tolerability profile to the patient.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614